

A Rare Case of Pulmonary Metastasis Exhibiting a Dual Phenotype of Cholangiocarcinoma and Pulmonary Adenocarcinoma: Emphasizing the Necessity for Meticulous Surveillance and Timely Intervention

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Abstract. Introduction: Metachronous neoplasms are characterized by the emergence of a new primary tumor following the oncologic or surgical treatment of another primary neoplasm, occurring more than 6 months after the initial diagnosis. Secondary pulmonary lesions from extrahepatic cholangiocarcinoma are infrequent and associated with a poor prognosis, with an annual survival rate below 12.7%. The synchronicity between a cholangiocarcinoma metastasis and a primary pulmonary tumor is exceedingly rare, and the carcinogenic mechanisms involved in the development of multiple neoplasms remain largely unknown. **Case Presentation:** We present the case of a 70-year-old patient with a history of cardiovascular and metabolic diseases, who has been under our clinic's care since 2018 for distal choledochal adenocarcinoma. The patient underwent a Whipple's cephalic pancreatoduodenectomy, revealing a mixed biliary-intestinal histology and received adjuvant chemotherapy. Periodic evaluations in our oncology department led to the discovery in August 2022 of multiple bilateral nodular pulmonary lesions with heterogeneous imaging aspects, suggesting a primary pulmonary lesion with metastases in the contralateral lung. A minimally invasive biopsy of a peripheral pulmonary lesion identified cellular morphology indicative of non-small cell carcinoma. However, immunohistochemistry revealed the lesion's mixed nature, comprising both biliary and pulmonary components. **Discussion:** A multidisciplinary approach is crucial for managing multiple neoplasms. Tailored treatment strategies, adapted to the complex characteristics of the pathology, are necessary. Vigilant monitoring and prompt intervention in managing multiple neoplasms are essential for improving their prognosis.

Keywords: Biliary tract, metastasis, lung, multidisciplinary treatment

Background

The development of a new primary tumor more than 6 months following the treatment of an initial primary neoplasm is known as a metachronous neoplasm. This is in contrast to synchronous neoplasms, which are diagnosed within 6 months of the initial cancer. The occurrence of secondary pulmonary lesions

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stemming from extrahepatic cholangiocarcinoma is observed in 4.1% to 11.3% of cases, with only a 12.7% chance of survival after one year¹. Representing 85% of all primary lung cancers, NSCLC also accounts for a 2.97% incidence of secondary lesions in the contralateral lung^{2,3}. In this report, we detail a case involving a 70-year-old patient who developed a secondary pulmonary lesion displaying characteristics of both cholangiocarcinoma (CC) and pulmonary adenocarcinoma.

Case presentation

A 66-year-old male presented to our hospital's emergency unit with symptoms of scleral and skin jaundice, fever, loss of appetite, and epigastric pain. Laboratory tests indicated biliary sepsis with features of inflammatory, cholestatic, and anabolic syndromes, including elevated conjugated bilirubin levels at 10.64 mg/dL. Abdominal CT imaging revealed a contrast-enhanced periampullary lesion and dilation of both intrahepatic and extrahepatic bile ducts, with no signs of local invasion or lymph node involvement.

The patient was admitted to the gastroenterology clinic, where an endoscopic retrograde cholangiopancreatography (ERCP) identified a periampullary ulceration. Biopsies were conducted, and three 8.5Fr/7cm stents were placed, resulting in bile drainage. The carbohydrate antigen 19-9 was measured at 119 UI/mL, with other markers within normal ranges. Histopathological analysis identified a moderately differentiated adenocarcinoma.

The case was reviewed by the tumor board, which recommended surgical resection. A Whipple-type cephalic pancreatoduodenectomy was performed (figure 1). The final pathological diagnosis was a moderately differentiated adenocarcinoma of the distal choledoch with a mixed biliary and intestinal phenotype and one positive lymph node, classified as pT2N1G2L1V0Pn0 (AJCC – 8th edition) and pT3N1G2L1V0Pn0 (WHO – digestive 2010), without vascular or perineural invasion.

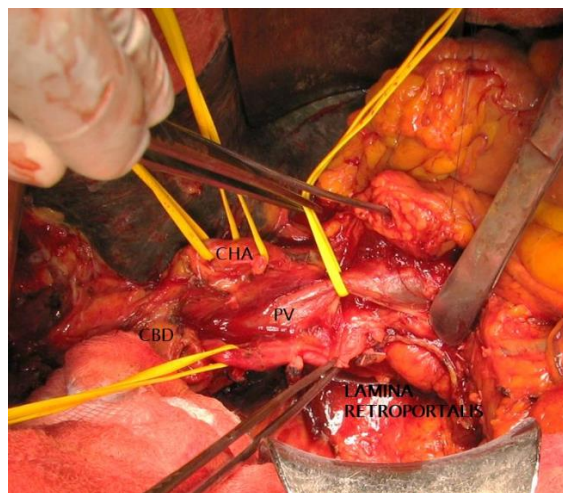


Fig. 1. Intraoperative aspect

The patient underwent adjuvant chemotherapy, comprising six cycles of Cisplatin and Gemcitabine over six months, followed by strict monitoring. Three years later, the oncology department detected multiple bilateral nodular lung lesions. A contrast-enhanced tumoral nodule was discovered in the left lower lobe, involving the left inferior pulmonary vein and completely obstructing the left inferior bronchus, encroaching upon the aorta and esophagus. Additional nodules in the contralateral lung were found in the right upper lobe (the largest measuring 15.5x9.5 mm) along with mediastinal lymphadenopathy (the largest measuring 25x10 mm) (Figure 2). The serological tumor biomarker CA 19-9 was over 1600 U/mL.

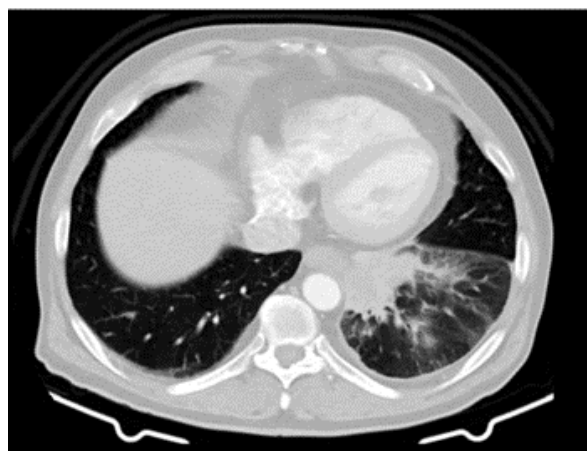




Fig. 2 CT images of pulmonary tumor

A biopsy was performed on a peripheral nodule due to the deep location of the primary tumor. Pathological examination confirmed a non-small cell carcinoma. Immunohistochemical analysis revealed the biliary nature of the lesion (CK7 positive, TTF1 negative, Napsin A negative, CK 19 negative, CK 20 negative, CDX2 negative, Glypican-3 negative, no endothelial growth factor EGFR mutations, PD-L1 under 1% and anaplastic lymphoma kinase (ALK) negative). The pathology result indicated a moderately differentiated pulmonary adenocarcinoma with an unspecific phenotypic profile, without completely excluding its

secondary nature in the context of the patient's history of extrahepatic CC.

Following the diagnosis, the patient began chemotherapy treatment with Cisplatin and Gemcitabine showing a favorable response. Figure 3.



Fig. 3: images of pulmonary tumors after one month of chemotherapy

In the subsequent month, the patient developed esophageal stenosis with an ECOG score of 2, resulting from external compression, and an uncovered prosthesis was inserted. A month later, the patient returned with recurring symptoms. Imaging explorations revealed stenosis below the lower end of the stent, and upper digestive endoscopy showed a luminal diameter of a maximum of 9 mm. The placement of a partially covered stent was indicated, but the patient passed away during hospitalization.

Discussions

The Surveillance, Epidemiology, and End Results (SEER) Program⁴ identifies any malignancy diagnosed within a 2-month period following the initial cancer as synchronous. In contrast, the International Agency for Research on Cancer (IARC) defines malignancies diagnosed within a 6-month period from the initial cancer as synchronous. This notable disparity in nosologically definitions leads to significant variations in the epidemiological profile and clinical interpretation of multiple primary neoplasms cases⁵. From an epidemiological standpoint, inconsistent definitions lead to unreliable interpretations and comparisons of data. Clinically, real-world experiences suggest that a two-month interval is insufficient for completing all necessary cancer diagnostic and staging procedures, consequently increasing the relative incidence of recorded metachronous malignancies. By extending the synchronous malignancies timeframe to 6 months, IARC's definition more closely aligns with the natural progression of cancers and also supports the clinical-biological rationale behind secondary prevention strategies.

Extrahepatic bile duct neoplasms encompass tumors developed distal to the convergence of the intrahepatic bile ducts, including perihilar lesions, distal choledochal, and gallbladder lesions. In the United States, the estimated incidence for 2023 accounts for 0.6% of all malignancies and 3.5% of gastrointestinal neoplasms⁶. The incidence of secondary pulmonary lesions following surgically resected extrahepatic CC ranges from 8 to 11.3%⁷, with a one-year overall survival rate of 12.7% compared to 43.3% in patients without metastasis¹.

In terms of immunohistochemistry, CC is commonly positive for CK7 and CK19, while it shows a lack of expression for CDX2 and CK20. To date, no genetic syndromes have been specifically associated with CC. The genetic profile of CC often includes mutations in the KRAS, p16/CDK2NA, TP53, and SMAD4 genes. Furthermore, the ERBB2/Her2Neu gene amplification is detected in about 20 to 30% of CC cases⁸. For the patient in question, the immunohistochemical tests were positive for CK7.

Lung cancer accounted for 11.4% of the total number of neoplasms diagnosed globally in 2020, ranking it second in prevalence while leading in mortality (occupying the first position) with 18% of total cancer-related deaths as reported by the WHO⁹. Non-small cell lung carcinoma (NSCLC) comprises 84% of primary lung neoplasms². In 2015, Morris ZS et al. conducted a study on 173,640 patients, identifying 5,161 (2.97%) cases of contralateral secondary lesions (M1a) with a three-year overall survival rate ranging between 23 and 6%, depending on the nodal stage³.

Immunohistochemistry techniques play a pivotal role as diagnostic and screening tools in cancer. Specific markers for pulmonary adenocarcinoma, such as TTF-1 (NKX2-1) clone 8G7G3 and Napsin A, are well-documented¹⁰. Immunohistochemistry can also be employed to detect certain genetic alterations that are amenable to targeted molecular therapies. Genetic changes observed in NSCLC include ALK translocation¹¹, ROS1 rearrangement¹², and EGFR mutations¹³. Other notable alterations are KRAS G12C mutation¹⁴, BRAF V600E¹⁵, NTRK 1/2/3 gene fusion¹⁶, MET exon 14 mutation¹⁷, RET rearrangement¹⁸, and ERBB2 (HER2) mutation¹⁹.

Immunosuppression in the context of pulmonary adenocarcinoma can be assessed through immunohistochemical methods. PD-L1 (CD274) acts as an immune modulator that promotes immunosuppression by binding to and inactivating PD-1 (programmed cell death protein 1)²⁰.

The immunohistochemical tests conducted on the biopsy specimen were negative

for the presented markers, and PD-L1 was below 1%, which is why the patient is not eligible for specific therapy.

Guidelines advocate for the testing of these molecular and immune biomarkers in all patients with NSCLC to determine their eligibility for targeted therapies or immunotherapies. This recommendation is grounded in data indicating an enhancement in overall survival for patients receiving targeted or immunotherapies compared to traditional chemotherapy regimens. Biomarker testing is advised for eligible patients with stage IV disease, including metastatic disease. The testing of specific biomarkers is also now advised for eligible patients with early-stage NSCLC who are candidates for surgical intervention²¹.

Radiation therapy (RT) is advised for localized symptom management or prophylaxis, targeting issues like pain, hemorrhage, or blockages. In cases of isolated or confined metastatic sites (oligometastases), such as in the brain, lungs, or adrenal gland, administering definitive or consolidative local treatment can extend survival in a select group of patients. This approach is most effective in patients who are in good physical condition and have undergone comprehensive treatment for the disease²².

Carbohydrate antigen 19-9, synthesized by the pancreatic and biliary ductal cells, as well as the epithelial cells of the stomach, colon, uterus, and salivary glands, is notably present in a broad spectrum of both benign and malignant conditions, extending beyond the gastrointestinal tract. Its overexpression is observed in various cancers, including those affecting the pancreas, biliary and hepatocellular systems, gastrointestinal tract, urinary system, lungs, gynecological organs, thyroid, and salivary glands²³.

Particularly in cases of extrahepatic CC, levels of CA 19-9 exceeding 103 U/L have been identified as significant indicators for assessing patient survival and the likelihood of metastasis²⁴.

Regarding lung cancer, CA 19-9 has been recognized for its utility in the diagnostic process, staging, and determination of prognosis, as well as in forecasting complications and the recurrence likelihood in NSCLC subtypes²⁵.

Conclusion

In the era of precision medicine, effectively treating metachronous lesions remains a significant challenge, highlighting our limited understanding of this pathology. The scarcity of comprehensive data on patients with multiple primary lesions complicates the management of such patients, presenting a formidable challenge for healthcare providers.

Conflict of interest. The authors have declared that no competing interests exist.

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